

Lack of Interaction Between Systemic Lupus Erythematosus-associated Polymorphisms in *TYK2* and *IRF5*

To the Editor:

These are exciting times for the genetic investigation of systemic lupus erythematosus (SLE), characterized by the discovery of many reproducibly associated loci¹. Further progress will require research in many different directions, including investigation of how the effects of each locus integrate between them and with environmental exposures to cause SLE. We read with interest the report by Hellquist, *et al*² that showed evidence of significant epistatic interaction between 2 SLE-associated loci, *IRF5* and *TYK2*. The first is a definitively confirmed SLE susceptibility locus with one of the strongest, albeit complex, effects. The latter has been more contentious, but its association with SLE is becoming clearer^{2,3}. Epistasis means that risk in subjects with susceptibility alleles at the 2 loci significantly exceeds the sum of the risks at each locus. This was rightly interpreted to mean that the 2 loci impinge in the type 1 interferon pathway², which is an important insight because *TYK2* codes for a Janus kinase that is involved in multiple cytokine signaling pathways in addition to this one⁴. Also, demonstration of epistasis between 2 SLE loci is of importance because its absence has been the rule for SLE genetic factors⁵ and for most genetic factors of other complex diseases^{6,7}. What is common is the contribution to total risk of the different disease alleles in a purely additive way, without any interaction. Therefore, we were interested in replicating the epistatic interaction described by Hellquist, *et al*² with the SLE data available to us.

We had already genotyped the relevant single-nucleotide polymorphisms (SNP), rs2304256 in *TYK2*³ and rs10954213 in *IRF5*⁸, in a large collection of patients with SLE and controls. These 2 SNP were associated with SLE in our studies ($p = 2.5 \times 10^{-5}$ and 0.015, respectively) with risk alleles that were coincident to those found by Hellquist, *et al* (who reported $p = 10^{-4}$ and $p = 0.004$, respectively). We have data for the 2 SNP in 419 SLE subjects and 454 controls. The same type of analysis done by Hellquist, *et al*², that is, a comparison between the fit to the data of logistic regression models with and without an interaction term, showed no differences (Table 1). As a more exhaustive and sensitive test, we also conducted analysis with the LASSOC software⁹. This approach compares a range of specific genetic models with and without interaction and does not require statistical significance to discriminate between models, but only differences according to the less stringent Akaike's Information Criterion (AIC). The best model has the lowest AIC value, which means that it has the best fit to the case-control genotypes with the highest combination of likelihood and parsimony. These analyses indicated that the best model included the independent contribution of the 2 loci without any interaction, although models with interaction terms were not much worse (Table 1). Therefore, we did not confirm the epistatic interaction that Hellquist and colleagues have described.

As a complementary analysis, we checked whether there was statistical evidence of interaction between *TYK2* and *IRF5* using other SNP in *IRF5*. These SNP were rs10488631 (which in some studies¹⁰ has been replaced

by its proxy, rs2070197) and rs729302. The first SNP showed the strongest association ($p = 4.8 \times 10^{-20}$) with SLE in our study⁸ and others¹⁰ and accounts for association of many other SNP in the gene, including rs10954213^{8,10}. The second, rs729302, is an SNP in the promoter region of *IRF5* that was independently associated to SLE in our samples ($p = 1.6 \times 10^{-9}$). Neither of the 2 SNP showed evidence of interaction with the rs2304256 SNP of *TYK2*, either with an analysis as done by Hellquist, *et al*² or with LASSOC (Table 1). These comparisons are more powerful than models with rs10954213 because the 2 *IRF5* SNP are much more strongly associated to SLE susceptibility and because we have data for 3-fold more samples: 1223 cases and 1300 controls.

Our results did not show any statistical evidence of interaction between SLE-associated SNP in *TYK2* and *IRF5*. As a consequence, we should continue to consider that these 2 SLE genetic factors can contribute to disease susceptibility by independent pathways, unless other genetic studies replicate the epistatic interaction or functional studies support the interaction. Similar interaction analysis for other genetic factors and in other sample collections will unravel the influence of epistatic interaction in SLE susceptibility, but current evidence does not support an important contribution⁵ (Suarez-Gestal, *et al*, unpublished data).

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Table 1. Lack of epistatic interaction between the SLE-associated SNP in *TYK2* and *IRF5*.

	SNP		No. of Subjects		Models with or without Interaction*		LASSOC Models **	
	<i>TYK2</i>	<i>IRF5</i>	SLE	Controls	Best Model	p	Best Model	AIC to Interaction
Hellquist ²	rs2304256	rs10954213	277	356	With interaction	0.014	—	—
Our data ^{3,8}	rs2304256	rs10954213	419	454	No difference	0.68	Additive [†]	1.83
	rs2304256	rs10488631	1223	1300	No difference	0.3	Additive	1.98
	rs2304256	rs729302	1223	1300	No difference	0.88	Additive	0.94

* Multivariate logistic regression models with and without an interaction term were compared as in Hellquist, *et al*². The models did not specify any mode of inheritance. P values were obtained with the likelihood ratio test. ** Comparison of the specific inheritance models included in LASSOC⁹. Akaike's Information Criterion (AIC) was used to classify the models. A value of AIC > 2 indicates a meaningful difference. † Additive: model with additive effects of each SNP, without dominance or interactive components. SNP: single-nucleotide polymorphisms.

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